REMARKS

Claim Status

Claims 1, 13, 14, 18-20, 23 and 24 have been amended. Claims 2, 4-6, 12, 15-17, and 25 have been cancelled. Claims 1, 3, 8-10, 13, 14, 18-20 and 22-24 are thus pending in this application.

Claim 1 has been amended to incorporate the limitations from canceled claims 2, 4 and 6, and is narrowed to recite a method of treating Non-Hodgkin's lymphoma by intravenous or intrarterial injection of monoclonal antibody 81C6 antibodies that bind to the epitope bound by monoclonal antibody 81C6. Because claim 1 as amended incorporates limitations from canceled claims 2, 4 and 6, it does not recite new subject matter.

Claims 13, 14, 18-20, 23 and 24 have been amended to depend from claim 1. Claim 23 has been amended to recite the method of claim 1 "wherein retention of said antibody in the lymphoma is at least two-fold greater compared to normal tissue."

No new matter has been introduced in these amendments. Upon entry of these amendments, claims 1, 3, 8-10, 13, 14, 18-20 and 22-24 will be pending. Entry and consideration of these amendments is respectfully requested.

Rejection of Claims 4, 12-22 and 24 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims reciting monoclonal antibody 81C6 (now claims 1 and 22, and those claims depending therefrom) under 35 U.S.C. § 112, first paragraph, as failing to provide adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

Applicants continue to respectfully disagree with this assertion.

As previously noted, the present invention is directed to the new use of a **known** compound. In particular, the anti-tenascin monoclonal antibody 81C6 was described in U.S. Patent No. 5,624,659 to Bigner et al. A review of the patent file reveals that a Sequence Listing under 37 C.F.R. §1.821(c) for the nucleotide and amino acid sequences described in the specification was submitted during prosecution of the application. By providing the relevant sequences and the synthesis of specific antibodies for use in the patented invention, one of ordinary skill in the art is provided a repeatable method for obtaining the 81C6 antibody. Accordingly, since the present invention is directed to a new use of this compound, Applicants respectfully submit that a deposit of the hybridoma that produces the molecule designated as antibody 81C6 for patent purposes is not required in this instance where the cell lines can be reproduced without "undue" experimentation.

Accordingly, Applicants respectfully submit that the pending claims comply with the written description requirement and the enablement requirement of 35 U.S.C. §112, first paragraph, and Applicants respectfully request withdrawal of these rejections.

However, in order to expedite prosecution, Applicants are willing to deposit the hybridoma that produces the molecule designated as antibody 81C6 in a recognized depository, once the Examiner has indicated that the present claims are otherwise in condition for allowance. Once the deposit has occurred, Applicants will provide the U.S. PTO with a verified statement corroborating that the deposit was made.

Rejection of Claims 1-6, 8-22, 23 and 24 Under 35 U.S.C. § 103(a) -- Obviousness

Claims 1-6, and 8-24 stand rejected for obviousness over the U.S. Patent 5,624,659 (Bigner et al.; "*Method of treating brain tumors expressing tenascin*") (the '659 patent), in view of Rizzieri et al., "*Markers of Angiogenesis, Factor VIII and Tenascin, Correlate with Disease Activity in Patients with Non-Hodgkin's Lymphoma*" Abstract #4339, Blood, vol. 94(10), part 2, supplement 1, p. 4339 (1999) ("*Rizzieri 1999*").

The Examiner states that the '659 patent teaches methods of treating solid and cystic tumors using the radiolabeled monoclonal antibody 81C6. The Examiner acknowledges that '659 does not teach a method of treating lymphomas, but asserts that *Rizzieri 1999* teaches that expression of tenascin is elevated in Non-Hodgkins Lymphoma patients. The Examiner asserts that it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the claimed invention to treat lymphomas with the therapeutic monoclonal antibody of the '659 patent. In addition, according to the Examiner, one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success, because the '659 patent teaches that any tumor that expresses tenascin could be treated with the therapeutic MAb 81C6 and *Rizzieri 1999* states that "the increase in tenascin expression [in Non-Hodgkin's lymphomas] suggests systemically delivered anti-tenascin antibody may be an effective form of therapy."

Applicants respectively disagree and assert that the pending claims, as amended, would not have been obvious.

For a claim to be obvious under 35 U.S.C. § 103(a), three criteria must be satisfied:

1. there must be some suggestion or motivation to combine or modify the cited references;
2. there must be a reasonable expectation of success of combining or modifying the cited references; and
3. the combined references must teach each and every limitation of the claimed invention.

Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000).

A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Also, rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*in banc*).

In addition, it is well established law that the proposed combination cannot render the prior art unsatisfactory for its intended purpose. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984) and MPEP 2143.01. If the proposed combination of references would change the principle of operation of the prior art invention being modified, then the references are not sufficient to render the claims obvious (*In re Ratti*, 270 F.2d 819 (CCPA 1959); MPEP 2143.01).

A. The Cited Prior Art Does Not Teach or Suggest the Claimed Invention

The current claims, as amended, call for a method of treating ***Non-Hodgkin's*** lymphoma by ***intravenous or intra-arterial injection of radiolabeled monoclonal antibody 81C6 or antibodies that bind to the epitope bound by monoclonal antibody 81C6***.

Neither the '659 patent nor *Rizzieri*, taken alone or together, teach or suggest the claimed invention. The '659 patent teaches a method for treating brain cancer, not Non-Hodgkin's lymphoma, and teaches direct deposit of the 81C6 antibody into the area requiring treatment, rather than intravenous or intra-arterial injection. *Rizzieri* does not teach a method of treating cancer using radiotherapy and does not mention the 81C6 antibody.

Therefore, the combination of the cited references would not enable one of ordinary skill in the art to arrive at the present invention directed to methods of treating Non-Hodgkin's lymphoma by injecting radiolabeled monoclonal antibody 81C6 or antibodies that bind to the epitope bound by monoclonal antibody 81C6 intravenously or intra-arterially.

Put more simply, one of ordinary skill in the art, when seeking an effective method for treating Non-Hodgkin's lymphoma, would not look to a ***different*** method (albeit one that uses the claimed antibody) of treating a ***different*** type of cancer (brain cancer).

Accordingly, Applicants respectfully submit that claims 1, 3, 8-10, 13, 14, 18-20 and 22-24, as amended, are not obvious under 35 U.S.C. § 103(a) in view of the '659 patent in combination with *Rizzieri 1999*, and Applicants respectfully request withdrawal of these rejections.

B. The Claimed Invention Yields Unexpected and Improved Results

As stated above, a *prima facie* case of obviousness may also be rebutted by showing that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*in banc*). Also, as stated in the Manual of Patent Examining Procedure (M.P.E.P.), "Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." M.P.E.P. §716.02(a) (citing *Ex parte The NutraSweet* Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991)).

As shown above, one of ordinary skill in the art would not have any expectation of success when treating any cancer exemplified by tumors that express tenascin by injecting an anti-tenascin antibody either intravenously or intra-arterially.

In addition, in a December 8, 2005 Amendment in this case, Applicants set forth other arguments that the claimed method yields unexpected results, based on statements made in a October 7, 2004 Declaration by inventor David A. Rizzieri, namely 1) the rapid uptake of ^{131}I anti-tenascin chimeric 81C6 monoclonal antibody in the liver and marrow and a slower and enhanced uptake in selected tumor sites as opposed to normal organs; (2) at least 2-fold greater retention of the radiolabeled antibody in lymphomas as compared to normal tissue; (3) the estimated average

absorbed dose to selected tumors of ^{131}I anti-tenascin chimeric 81C6 monoclonal antibody was higher than that obtained from ^{131}I-tositumomab (tositumomab (Bexxar®) is a commercially available labeled antibody for treatment of lymphoma); and (4) the instant radiation dose delivered to the tumor per unit of administered activity was higher than that seen with ^{131}I-tositumomab and consequently these results indicate substantially longer tumor retention than reported for other antibodies evaluated for radioimmunotherapy (tositumomab, anti-CEA hMN-14, anti-TAG72 CC49, A33,17-1A, for example).

The Examiner has rejected applicants' assertion that the claimed method yields unexpected results, contending that applicants' comparison of a radiolabeled anti-tenascin antibody with other radiolabeled antibodies fails because it is predicated on antibodies that are structurally different, bind different targets, and have different absorption rates and tumoricidal activities.

Applicants again respectfully disagree. These arguments were not put forth because Applicants were attempting to demonstrate that the 81C6 monoclonal antibody was a better antibody than those in the prior art. Rather, they were used to demonstrate that the claimed method of radiolabeled antibody-facilitated therapy targeted to tenascin is far superior than other methods employing the above-mentioned antibodies. Taken in the proper context, the information above demonstrates that the claimed method of treating lymphomas by intravenous or intra-arterial administration of a radiolabeled anti-tenascin monoclonal antibody yields significant, unexpected, and unobvious results. All of the above-mentioned antibodies are specific for cell surface antigens. Tenascin, on the other hand, is an extracellular matrix protein expressed in tumor stroma. The methods according to this invention represent the first intravenous use of a radiolabeled antibody directed toward a stromal target. *See Rizzieri* et al., "*Phase I Trial study of ^{131}I-labeled chimeric 81C6 monoclonal antibody for the treatment of patients with non-Hodgkin's lymphoma*" page 642, columns 1 and 2 (Clinical Observations, Interventions, And Therapeutic Trials **104**:642-648 (2004) (*Rizzieri 2004*, submitted as **Exhibit 4** in Applicants' September 11, 2006 response to the Match 11, 2006 Office Action in this case). Based on the negative results when ^{131}I-labeled anti-

tenascin MAb 81C6 was evaluated for systemic administration for treating brain cancer, and considering that the claimed method of treating lymphoma represents pioneering work, it was completely unexpected that intravenous administration of radiolabeled MAb81C6 resulted in enhanced uptake in selected tumor sites as opposed to normal organs and at least 2-fold greater retention of the radiolabeled antibody in lymphomas as compared to normal tissue, and also that therapeutic levels of radiation were absorbed better than ^{131}I-tositumomab and retained longer than reported for tositumomab and other antibodies evaluated for radioimmunotherapy. This represents a significant practical advantage other methods of treating lymphomas, because target uptake and retention are critical components of successful therapy employing radiolabeled antibodies.

Accordingly, at least in view of these unexpected results clearly presenting a significant and practical advantage, Applicants respectfully submit that claims 1, 3, 8-10, 13, 14, 18-20 and 22-24, as amended, as amended, are not obvious under 35 U.S.C. § 103(a) in view of the '659 patent in combination with *Rizzieri 1999*, and Applicants respectfully request withdrawal of these rejections.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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